SPECIFIC PREVENTIVE AND CURATIVE THERAPY, WITH SPECIAL REFERENCE TO GASEOUS GANGRENE

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THERE are two kinds of immunity—natural and acquired. Natural immunity to certain diseases is sometimes the common property of a whole species of animal, as in the case of the immunity of fowls to tetanus infection. Immunity may be acquired either through an attack of the disease, in which it may persist for a lifetime, or through protective inoculation with the bacterial bodies or their products. In the case of vaccination with the killed or attenuated bacterial bodies an active immunity is set up in the person vaccinated, his own body cells reacting in such a way to the bacteria introduced that actively immune substances, antagonistic to the specific bacteria injected, are produced within his body and exist in considerable quantities in his blood stream. Such an immunity, while not nearly so enduring as that acquired from an attack of the disease, may last for several years, and such a person, although he has never had the disease in question, is said to be actively immune to it.

Immunity may also be conferred upon one individual by injecting into his blood stream large quantities of the serum of another individual actively immunized to the disease. Such an immunity is said to be passive, because the body cells of the person inoculated take no part in it, the degree of immunity depending wholly upon the concentration of immune substances, or "antibodies," in the serum injected. Immunity of this sort is, of course, very fleeting in character. It can be maintained only by repeated injections of the immune serum and is applied as a precautionary measure where there is a possibility of infection, as in tetanus, or as a curative agent in an acute disease like diphtheria.

Immune sera for therapeutic use are usually produced in horses. Such sera may be of two kinds. They may be produced with the bacterial bodies themselves, in which case they are called antibacterial sera; or they may be produced with

sterile filtrates containing the soluble toxic products of the bacteria, when they are known as antitoxic sera, or antitoxins. An antibacterial serum acts directly upon the specific invading microorganism and prepares it for destruction by the body cells, while an antitoxic serum, by neutralizing the toxin produced by the bacteria during growth, inhibits that growth and prevents its spread, thus giving the body a chance to destroy the bacteria. An example of an effective antibacterial serum is that used in the treatment of cerebrospinal meningitis. The meningococcus, which is the specific organism against which this serum is prepared, does not secrete in cultures a true bacterial toxin, but there can be prepared in horses, by the injection of the bacterial bodies, a potent serum which has proved extremely valuable in the treatment of this disease.

An example of an antitoxic serum is that prepared against diphtheria. Such a serum is produced in horses by the injection of the sterile filtrate from broth cultures of the diphtheria bacillus. This organism secretes, when grown in a suitable medium, a true soluble toxin which may be filtered through the finest filters and still prove fatal for guinea pigs in very small doses, after all the bacteria have been removed. It is only with a true secretory toxin like this that an antitoxic serum can be produced. The bacterial toxins so far shown to be of large practical importance are those of diphtheria and tetanus, and the sera prepared with these toxins are the only true antitoxins at present in general use. Certain antibacterial sera, notably that prepared with the Shiga dysentery bacillus, possess a degree of antitoxic power in addition to their antimicrobial properties, but it is insufficient to warrant their being classed with the true antitoxins.

The terms "vaccine" and "serum" are often confused, even used synonymously by laymen and physicians as well. They are very different in their biologic natures and fields of usefulness. It is considered expedient, therefore, to state here briefly the difference between a "vaccine" and a "serum." A vaccine, strictly speaking, is a suspension of the killed or attenuated bacterial bodies in some sterile fluid such as physiological salt solution. In the case of a disease like smallpox, where no visible bacterial agent can be demonstrated, the vaccine is made from the attenuated "virus," which is the living infectious agent. A serum, on the other hand, is the clear yellowish residual fluid remaining after blood has been allowed to clot and all the corpuscles and the fibrin have separated out. It contains none of the bacteria or toxin with which it may have

been rendered immune in the living animal body, but only those reaction products of the animal to the bacteria or toxin injected that make it a fit therapeutic agent for use against the organism that produced it. It differs from a vaccine in containing the reaction products of the animal to the bacteria or their toxins rather than the bacterial bodies themselves. The most widely and successfully employed vaccines are those prepared against smallpox, rabies, typhoid and paratyphoid fever. Their injection incites a reaction on the part of the body cells of the inoculated person and thereby confers an active immunity which is capable of warding off infection for a period of two or more years. Immune sera, such as diphtheria and tetanus antitoxins, confer, on the other hand, a passive immunity which lasts only about two weeks. Vaccines find their greatest usefulness as preventive agents, while antitoxins are of great value as both curative and preventive agents. Tetanus antitoxin is very widely used to prevent lockjaw after certain predisposing injuries; it possesses healing power also. Diphtheria antitoxin may be used to ward off the disease after known exposure to infection, but it is especially efficacious as a curative agent.

The organism with which the present article[1] is mainly concerned is known as *Bacillus welchii.* It was first described in 1892 by Welch and Nuttall, who found it in a human case at autopsy and gave to it the name of *Bacillus aerogenes capsulatus* —the "gas-forming capsulated bacillus." Since then the organism has been described in human infections by men of various nationalities and has been given a different name by almost every investigator. In the United States it is known as *Bacillus welchii*; in France as *Bacillus perfringens*; in Germany as *Bacillus phlegmonis emphysematosae,* and an English investigator named it *Bacillus enteritidis sporogenes.* These are only a few of the names that have been given this same organism by the different men who have worked with it. The confusion arising from these variations is obvious.

Morphologically *Bacillus welchii* is a large, plump rod, with the ends very slightly rounded. It occurs singly or in pairs, and in infected tissues is often found in long chains or filaments. Both in artificial cultures and in infected tissue it forms large amounts of gas and acids. The gas is chiefly hydrogen and carbon dioxide. The acids are a mixture of organic acids, chiefly butyric. Both acids and gas are formed very readily in

[1] A fuller and more technical treatment is given in the paper by Bull, C. G., and Pritchett, Ida W., entitled "Toxin and Antitoxin of and Protective Inoculation Against *Bacillus welchii*" and published in the *Journal of Experimental Medicine*, 1917, XXVI., 119.

beef infusion broth, to which glucose has been added, the acidity increasing with the amount of glucose. A 3 per cent. glucose broth culture sometimes becomes 7 per cent. acid in three or four days. Growth in milk, to which litmus has been added, presents a characteristic appearance. The blue litmus milk first becomes pink, due to the formation of acids. Then the curd forms and is bleached, and finally the gas given off blows the curd to pieces, and all the whey is expressed. In such a culture we have manifestations of two of the chief characteristics of *Bacillus welchii,* namely the formation of acid and of gas.

This organism does not develop unless the oxygen has been at least partly removed from the medium in which it is grown, either by boiling or by exhaustion in a vacuum jar. It is therefore classed among the bacteria known as anaerobic, although it is not as strictly anaerobic as the tetanus bacillus or the virus of poliomyelitis. It is very widespread in nature, existing normally in the intestinal tracts of man and animals, in most samples of market milk, in dust, in wool, on the skin—in fact, almost everywhere, It is able to maintain itself under unfavorable circumstances and to grow again when the proper conditions are provided through its ability to form spores. These spores are highly resistant to influences that are fatal to the ordinary growing or vegetative form of the organism. They can stand without serious injury a degree of heat that kills all the vegetative forms. They require no nourishment and may remain alive and virulent for a very long time. This ability to form spores is the common property of a great many bacteria, of which fortunately only a few—tetanus, anthrax, malignant edema, *Bacillus welchii,* and possibly others—are pathogenic for man.

With an organism as widely distributed as *Bacillus welchii,* infection may easily occur. It has been cited as the cause of pathological conditions as unrelated as diarrhœa and inflammation of joints, but it is primarily an invader of muscular tissue, rarely gaining access to the general circulation during life. Furthermore, the muscular tissue must be lacerated and the wound deep to provide the most ideal conditions for its growth. Healthy muscle is usually attacked only after the bacteria have invaded an adjacent crushed and torn area. When infection is once established in such a crushed muscle, it spreads very rapidly. Large amounts of gas are formed, distending the tissues and escaping in bubbles into the open wound. There is an escape of fluid from the vessels into the infected tissues, producing what is known as an edematous

condition. The tissues in and around the wound are so injured by the growth of the bacteria that they die and become gangrenous. If nothing is done to check its progress, the infection spreads rapidly, gas becomes evident in tissues far removed from the primary focus of infection, death of the muscles and gangrene progress rapidly, and collapse and death soon follow. This is the condition produced by *Bacillus welchii* in lacerated muscular tissue and, on account of the large amount of gas formed in the necrotic muscles, is known as gaseous gangrene.

The incidence of gaseous gangrene in civil life is not high. A certain number of cases is always to be found in city hospitals, due largely to industrial injuries and street accidents, but they form a very small percentage of the total yearly hospital records. Under war conditions, however, gaseous gangrene becomes a very different problem. A very large number of the wounds received on the battlefields of Europe are infected with the gas bacillus. The country through which the armies are fighting has been intensively cultivated for centuries, and the rich earth is necessarily heavily infected with all manner of intestinal bacteria, the spores of tetanus and gas bacillus among them. Under the conditions of trench life the soldiers' uniforms become caked with this infected earth, and when shell wounds occur, a bit of cloth is usually carried deep into the lacerated tissue, and ideal conditions are produced for the development of tetanus or of gaseous gangrene. The tetanus problem is well solved by the administration of a prophylactic dose of tetanus antitoxin to every wounded man at the first dressing station, to guard against a possible infection. By this means the incidence of tetanus, once so appalling, has been reduced to relatively few cases, but the tetanus antitoxin has no effect upon the development of gaseous gangrene, being specific for tetanus. The wounded must therefore take their chances of gas infection with all its awful consequences which the vastly improved methods of antisepsis and wound irrigation have not yet entirely abolished. There is every reason to believe, however, that the antitoxin whose discovery at the Rockefeller Institute was recently announced by Bull and Pritchett will be as effective in preventing gaseous gangrene as tetanus antitoxin is in preventing lockjaw, and also that it will exhibit curative properties.

The theories of the manner of the destructive action of *Bacillus welchii* in the infected animal body are almost as varied as its names. Some attribute its injurious effect to the absorption of toxic decomposition products from the infected

and disintegrating tissues. Others consider that the harmful effects are due to the large quantity of gas formed, which, being unable to escape, collects in the tissues, gradually cuts off the blood supply by the pressure it exerts and so causes death of the tissues; this dead tissue is then invaded by putrefactive bacteria which disorganize it, and so gaseous gangrene is established. Still others have maintained that the pathological condition is due to the irritating effect of the large amount of acids formed in the tissues and have claimed to be able to reproduce in animals identical lesions and death by injections of the pure organic acids. These are only a few of the theories that have been advanced to account for the pathology of gas infection. It remains to present the theory of the toxic action of the bacilli.

In undertaking a study of gaseous gangrene, one is struck by the fact that the infection, though essentially a local one, *i. e.*, confined to a more or less circumscribed area and rarely, if ever, gaining entrance to the blood stream, is yet capable of causing extreme prostration and death, sometimes within a very few hours after the appearance of the first symptoms. This leads one to compare it with other infections, such as tetanus and diphtheria, which are also purely local in character, and in each of which the active agent is known to be a very powerful toxin, secreted by the bacteria during the process of growth and disseminated through the body by means of the circulating blood. Although neither tetanus nor diphtheria presents the extensive destruction of tissues that we find in gas infection, the other points of similarity make it reasonable to suppose that like them *Bacillus welchii* might secrete a true soluble toxin which is its chief weapon of offense, and without which it would be powerless to cause the lesions typical of gaseous gangrene. This supposition led to an effort to reproduce in the test tube the ideal conditions for growth that we find in deep, lacerated wounds of the muscular tissues—namely, absence of oxygen and a supply of raw muscle.[2] To this end a 0.2 per cent. glucose beef infusion broth was made up, glucose being the chief muscle sugar and especially favorable for the growth of the gas bacillus. To tubes containing ten cubic centimeters of this sterile broth were added fragments of fresh sterile rabbit or pigeon muscle. These tubes are inoculated with a pure culture of *Bacillus welchii* and after being incubated over night at 37° Centigrade are filtered through sterile filters. The clear amber filtrate thus obtained contains the soluble toxic products of the gas bacillus. Such a filtrate is capable of causing, in very small doses, the

[2] Bull, C. G., and Pritchett, Ida W., *loc. cit.*

typical picture of gaseous gangrene—edema of the tissues, extensive necrosis of the muscles, and death. Its pathological effects can be differentiated from the infection itself only by the absence of bacteria and of gas. Like all true toxins, it does not immediately produce its effect, but requires a latent or an incubation period. Its toxic action is not affected by neutralization with sodium hydroxide, a fact which rules out the acid as the principal cause of the lesions. It conforms in every way to the requirements of a true secretory toxin similar to those of tetanus and diphtheria. Finally it has been possible to produce with it a potent antitoxic serum which will not only neutralize the toxin so that it produces no lesion, but will inhibit the growth of the bacteria in the body. It has been possible to treat successfully well established infections, so that the lesions healed completely. And most important of all, complete immunity of at least two weeks' duration against both the toxin and the live bacteria can be conferred upon guinea pigs and pigeons by injecting them subcutaneously with a small amount of antitoxin. The animals so treated are entirely refractory, during this period, to subsequent injections of toxin and of live culture that kill normal guinea pigs in a very short time. These facts point to the possibility of a serum prophylaxis for gas gangrene as effective as that already used in the prevention of tetanus.

Rabbits, goats, and horses have all been made to yield antitoxic sera by injecting them subcutaneously or intravenously with carefully graded doses of toxin. At present several horses and goats are in process of immunization. These animals are injected at regular intervals and are bled from time to time to test the amount of antitoxin present in their sera. These antitoxins are carefully standardized, the number of antitoxic units in a cubic centimeter of serum being determined for each bleeding. In this way a record is kept of the increase in antitoxic power of the serum of each animal.

It would appear, then, that there is every reason to look to the serum treatment for a profound decrease in the incidence of and fatalities from gaseous gangrene due to war wounds. The ideal condition would be to give a prophylactic or preventive dose of the antitoxin to all wounded men at the first dressing station as is now done with tetanus antitoxin. In this way it is fair to hope that the development of gaseous gangrene may be prevented in many or almost all cases, besides which the antitoxin appears to be of distinct value as a curative agent in cases of gaseous gangrene already developed.